



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2019-N-3369]

Evaluating the Clinical Pharmacology of Oligonucleotide Therapeutics; Establishment of a Public Docket; Request for Information and Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; establishment of a public docket; request for information and comments.

SUMMARY: The Food and Drug Administration (FDA or Agency) is establishing a public docket to collect comments on evaluating the clinical pharmacology of oligonucleotide therapeutics. There are many unique clinical pharmacology considerations concerning the development of oligonucleotide therapeutics; however, for the purposes of this request, the Agency is specifically interested in comments regarding the characterization of the effects of hepatic and renal impairment, drug-drug interactions, and immunogenicity on the pharmacokinetics of oligonucleotide therapeutics as well as the effects of oligonucleotide therapeutics on cardiac electrophysiology. Public comments will help the Agency develop recommendations for the design and conduct of studies important to the safe and effective use of oligonucleotide therapeutics and facilitate the regulatory assessment of such studies.

DATES: Although you can comment at any time, to ensure that the Agency considers your comment in our development of recommendations, submit either electronic or written information and comments by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments at any time as follows:

### *Electronic Submissions*

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

### *Written/Paper Submissions*

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

*Instructions:* All submissions received must include the Docket No. FDA-2019-N-3369 for "Evaluating the Clinical Pharmacology of Oligonucleotide Therapeutics; Request for Comments." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

*Docket:* For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Hobart Rogers, Office of Clinical Pharmacology, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, 301-796-2213, [Hobart.Rogers@fda.hhs.gov](mailto:Hobart.Rogers@fda.hhs.gov).

#### SUPPLEMENTARY INFORMATION:

##### I. Background

Oligonucleotide therapeutics typically are synthetically modified single- or double-stranded ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) that exert pharmacologic effects through a variety of mechanisms (e.g., altered splicing, RNA interference, immunomodulation, microRNA modulation). Compared to small molecule or biological products, oligonucleotide therapeutics have unique characteristics regarding their chemistry, pharmacology, sites of action, pharmacokinetic disposition, and pharmacodynamics. As a result, there may be special considerations for the design and conduct of clinical pharmacology studies to assess oligonucleotide therapeutics, such as those designed to evaluate the effects of organ impairment or drug interactions. Currently, none of FDA's currently published guidance documents on clinical pharmacology assessments contain specific recommendations for oligonucleotide therapeutics.

## II. Request for Information and Comments

Interested persons are invited to provide detailed information and comments on certain aspects of evaluating the clinical pharmacology of oligonucleotide therapeutics. This request focuses on oligonucleotide therapeutics designed to hybridize to a cognate RNA to elicit a pharmacologic effect. For all questions, organize any discussion by the type of oligonucleotide therapeutics (e.g., by chemistry or modification type). Please provide the rationale for your suggestions and include supporting data if available. FDA is particularly interested in responses to the following overarching questions:

### (1) Evaluating Drug-Drug Interactions (DDIs)

(a) Under what circumstances should clinical DDI assessment be warranted or not warranted for oligonucleotide therapeutics?

(b) In circumstances where DDI assessments are warranted:

(i) What types of DDI assessments are suitable and why (e.g., in vitro studies, dedicated clinical studies, cocktail studies, population pharmacokinetic analyses)? Please discuss the advantages, challenges, and limitations with each type of assessment.

(ii) What are the study design considerations (e.g., in vitro test systems, population, analytes) for the types of assessments discussed in item (1)(b)(i) above? Please describe the rationale for any design considerations proposed.

### (2) Evaluating the Pharmacokinetics in Organ Impairment

(a) Under what circumstances are organ impairment assessments for oligonucleotide therapeutics warranted or not warranted for:

(i) renal function

(ii) hepatic function

(b) In circumstances where organ impairment assessments are warranted:

(i) What types of assessments are suitable for renal and/or hepatic impairment and why (e.g., dedicated clinical studies, population pharmacokinetic analyses)? Please discuss the advantages, challenges, and limitations with each type of assessment.

(ii) What are the study design considerations (e.g., study population) for the types of assessments discussed in item (2)(b)(i) above for renal and/or hepatic impairment? Please describe the rationale for any design considerations proposed.

### (3) Evaluating Immunogenicity

(a) Under what circumstances are immunogenicity assessments of oligonucleotide therapeutics warranted or not warranted?

(b) In circumstances where immunogenicity assessments are warranted:

What types of assessments are suitable and why (e.g., antibodies against other components of the formulation, antibodies against a newly created "splice-altered" protein, neutralizing titers, cytokine measurements)? Please discuss the advantages, challenges, and limitations with each type of assessment.

### (4) Evaluating QT Prolongation

(a) Under what circumstances are cardiac electrophysiology assessments warranted or not warranted in the evaluation of oligonucleotide therapeutics?

(b) In circumstances where cardiac electrophysiology assessments are warranted:

What types of assessments are suitable and why (e.g., hERG inhibition assay, thorough QT assessment) in nonclinical or clinical studies? Please discuss the advantages, challenges, and limitations with each type of assessment.

(5) With regard to the four questions above, when a sponsor seeks to rely on previously generated data and information that it owns or to which it has a right of reference, what scientific findings may be applied across the sponsor's oligonucleotide therapeutics with shared characteristics (e.g., similar backbone modifications)?

FDA will consider all information and comments submitted.

### III. Electronic Access

Persons with access to the internet may obtain relevant clinical pharmacology guidances at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

Dated: August 2, 2019.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

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